

Stat5: from lactogenesis to tumorigenesis

Itamar Barash

Institute of Animal Science, ARO the Volcani Center Bet-Dagan, Israel

The signal transducer and activator of transcription (Stat5) is a cytoplasmic signaling molecule and a transcription factor which confers the effects of cytokines, polypeptide hormones and growth factors into transcriptional activity. In the mammary gland, Stat5 controls epithelial cell proliferation, lactogenesis, lactation and cell survival. In transgenic mice, we have shown that deregulation of Stat5 activity during the reproductive cycle results in parity-dependent development of mammary tumors in post-estropausal females. Overexpression of the native and constitutively active form of Stat5 cause mainly highly differentiated tumors, while its C-terminally truncated form induced mainly the poorly differentiated carcinomas. Several mechanisms may account to the oncogenic effect of Stat5. (i) DNA damage. Production of reactive oxygen species during the vulnerable stage of pregnancy induced significant DNA damage and cellular DNA damage response within three days. Chromosomal breakage, fragmentation and translocations occasionally result in tumorigenesis. (ii) Parity-dependent Histone modifications at the Stat5 binding sites in the cyclin D1 and bcl-x gene promoters during the reproductive cycle. These modifications expose individual cells to the deregulated effect of Stat5 which highly activates these genes. (iii) Silencing tumor suppressors and proliferation antagonists. These distinct metabolic consequences occur during tumor development and mediate the earlier effect of deregulated Stat5. Thus, in association with the protective effect of parity against breast cancer that was reported in epidemiological studies, parity-dependent deregulated levels and activity of Stat5 represent a long-term risk factor. Monitoring Stat5 activity in the breast during the vulnerable stage of pregnancy may help in reducing its oncogenic effect.

Biography

Itamar Barash has received his Ph.D from The Hebrew University of Jerusalem and completed postdoctoral studies at McGill University and the Weizmann Institute. He is the head of the Department of Ruminant Science and Genetics of the Institute of Animal Science of the Volcani Center. He has published more than 43 papers in reputed journals. The current research topics in his lab are: The role of Stat5 in normal mammary development and function and in tumorigenesis; amino acids acting as signal molecules in the mammary gland; Identification of stem cells in the bovine mammary gland.